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The relationship between the prognostic nutritional index and the clinical course of COVID-19: a single-center experience

Prognostik nütrisyonel indeks ve COVID-19 klinik seyri arasındaki ilişki: tek merkez deneyimi

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ABSTRACT

Aim: It was aimed to investigate the relationship between the prognostic nutritional index (PNI) and the clinical course in COVID-19 because the nutritional status is important in defense against infection.

Material and Method: 1579 patients who applied to the hospital inpatient clinic between 01/04/2020 and 30/11/2020 were included in the study. The PNI scores of the patients were calculated at the time of admission to the hospital. Comparisons were made between PNI scores of the patients and intensive care unit admission status, treatment results, length of hospital stay, and presence of pneumonia on thorax CT. Moreover, comparisons were made between PNI scores and C-reactive protein (CRP), neutrophil/ymphocyte ratio (NLR), CRP/albumin ratio.

Results: A total of 1579 patients (755 females and 824 males) were included in the study. The rate of admission to the ICU was significantly higher in males. The mortality rate of the study group was 9.4%. PNI scores were found to be significantly lower in patients who died and in patients admitted to the ICU. CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the intensive care unit, and in patients who died. There were a significant negative correlation between PNI score and CRP/albumin ratio levels.

Conclusion: PNI scores were found to be significantly lower in patients who needed admission to the intensive care unit and died due to severe COVID-19 than the others. In patients with a low PNI score, COVID-19 can be more severe and it may cause worse clinical outcomes.

Keywords: COVID-19, CRP/albumin ratio, neutrophil/lymphocyte ratio, prognostic nutritional index

ÖZ

Amaç: Enfeksiyona karşı savunmada beslenme durumunun önemli olması nedeniyle COVID-19'da prognostik beslenme indeksi (PNI) ile klinik seyir arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntem: 01/04/2020-30/11/2020 tarihleri arasında hastaneye başvuran 1579 hasta çalışmaya dahil edildi. Hastaların hastaneye başvuru anında PNI skorları hesaplandı. Hastaların PNI skorları ile yoğun bakıma yatış durumu, tedavi sonuçları, hastanede kalış süreleri ve toraks BT'de pnömoni varlığı arasında karşılaştırmalar yapıldı. Ayrıca PNI skorları ile C-reaktif protein (CRP), nötrofil/imfosit oranı (NLR), CRP/albumin oranı arasında karşılaştırmalar yapıldı.

Bulgular: Çalışmaya toplam 1579 hasta (755 kadın ve 824 erkek) dahil edildi. Erkeklerde yoğun bakıma kabul oranı anlamlı olarak daha yüksekti. Çalışma grubunun mortalite oranı %9,4'tü. Ölen hastalarda ve yoğun bakım ünitesine kabul edilen hastalarda PNI skorları anlamlı olarak daha düşük bulundu. Toraks BT'sinde pnömoni olan hastalarda, yoğun bakıma yatırılan hastalarda ve ölen hastalarda CRP ve CRP/albümin oranı anlamlı olarak daha yüksekti. PNI skoru ile CRP/albümin oranı arasında anlamlı negatif korelasyon vardı.

Sonuç: Şiddetli COVID-19 nedeniyle yoğun bakım ünitesine yatırılması gereken ve ölen hastalarda PNI skorları anlamlı derecede daha düşük bulundu. PNI skoru düşük olan hastalarda COVID-19 daha şiddetli seyredebilir ve daha kötü klinik sonuçlara neden olabilir.

Anahtar Kelimeler: COVID-19, CRP/albümin oranı, nötrofil/lenfosit oranı, prognostik beslenme indeksi

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious viral disease. The causative agent of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). SARS-CoV-2 is an enveloped RNA virus (2). In humans beings are the main route of transmission of SARS CoV-2 is virus-carrying respiratory droplets (3). Generally, COVID-19 patients develop symptoms 5-7 days after exposure. Common symptoms are fever, sore throat, cough, myalgia, headache, dyspnea, nausea and diarrhea. SARS-CoV-2 enters the cell by attaching to the angiotensin converting enzyme 2 (ACE2) receptor. The infection process begins with the binding of the viral envelope S protein of SARS CoV-2 to the ACE2 receptor in the cell membrane. The ACE2 receptor is found in the lungs, endothelium, heart, kidneys, brain and intestines (3). Therefore, all these organs can be a target of the virus and complications may occur in these organs.

The nutritional status of a person is important in defense against infection. Individuals with nutritional deficiencies are more susceptible to infectious diseases and worse clinical results may be seen in these individuals (4). Based on this, in studies conducted, malnutrition was found to be an independent risk factor for complications in hospitalized patients and was associated with higher mortality (5). Prognostic nutrition index (PNI) is a new risk score based on serum albumin and lymphocyte values, reflecting the immunological and nutritional status of the person. PNI has proven prognostic value in a variety of diseases, including cardiovascular diseases, infectious diseases and malignancies. It has been shown that low PNI score is associated with poor survival (6,7). It is not difficult to calculate this index as it only requires blood parameters and it is a cost-effective method.

COVID-19 continues to be a widespread public health problem all over the world today, and it also causes major social and economic problems. We think that the nutritional status of patients is very important in the course of infectious diseases. In this study, it was aimed to investigate the relationship between the PNI score of COVID-19 patients and the clinical course of the disease.

MATERIAL AND METHOD

For this study, written consent was obtained from the patients and was carried out with the the permission of Sancaktepe Sehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date:10/03/2021, Decision No: 2020/123). All human studies have been performed under the rules of 1964 Declaration of Helsinki.

The study was conducted on 1724 patients who applied to the inpatient clinic between 01/04/2020 and 30/11/2020. COVID-19 PCR test was performed on these patients who were admitted to the hospital with suspicion of COVID-19, blood was taken for the test, and thorax CT was planned. The diagnose of COVID-19 in patients had been confirmed by a positive result for SARS-CoV-2 RNA in nasopharyngeal swabs by using real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) before the patients was applied to the inpatient clinic. In all patients, gender, age, medical history, COVID-19 PCR test results, blood test results, thorax CT reports, hospitalization status and treatment results were examined. Patients over 18 years old with positive COVID-19 PCR test were included in the study. Patients under the age of 18, with negative COVID-19 PCR test result, in case of malignancy, pregnancy, and with severe endocrinological, nephrological, gastrointestinal, neurological, psychiatric diseases, hematological disease were excluded from the study. For these reasons, a total of 145 patients were excluded from the study. Finally, a total of 1579 patients were included in the study.

The PNI scores were calculated according to the results of the blood tests of patients at the hospital. For each patient, the PNI score was calculated based on this formula; PNI = [10 x albumin (mg/dL)] + [0.005 x lymphocyte count (per mm^3)] (8). Comparisons were made on whether there was a relationship between PNI scores of the patients and intensive care unit (ICU) admission status, treatment results (exitus/healed), length of hospital stay, and presence of pneumonia on thorax CT. Also, comparisons were made between PNI scores and the results of some other infection parameters such as C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), CRP/albumin ratio.

Statistical analysis: While evaluating the study data, the suitability of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro Wilks tests and the homogeneity of group variances was assessed by the Levene test. Descriptive statistical methods including percentage and mean±standard deviation (±SD) or median (interquartile range [IQR] were used to provide the basic features of the data, according to the evaluation of distribution for normality. Differences in the values of the variables between the groups were evaluated by the Mann–Whitney U test according to the results of normality tests. Chi-square test was used to analyze qualitative data. Spearman Correlation test was performed to evaluate the correlation between PNI scores and other parameters. The IBM SPSS (Statistical Package for Social Sciences; version 20.0 for windows, Chicago, USA) was used for statistical analyses, and $p<0.05$ was considered significant for all statistical analyses.

RESULTS

A total of 1579 patients (755 females and 824 males) were included in the study. The median age of the whole patient group was 54 [IQR:43-65] years. 85.9% of the patients had pneumonia on thorax CT, 87.9% of males and 83.8% of females had pneumonia on thorax CT. The rate of presence of pneumonia on thorax CT was significantly higher in males (p:0.022). 14.8% of all patients were admitted to the intensive care unit (ICU), 18.8% of males and 10.3% of females were admitted to the ICU. The rate of admission to the ICU was significantly higher in males (p<0.001). The mortality rate in the whole group was 9.4%. The mortality rate was 11.4% in males and 7.2% in females. The The mortality rate was significantly higher in males (p:0.004). There was no significant difference in ICU admission rates according to gender, but total length of hospital stay was significantly longer in males (p=0.006). CRP and CRP/albumin ratio levels were higher in males. There was no significant difference between PNI scores and neutrophil/lymphocyte ratio (NLR) levels according to gender. (**Table 1**)

When we compare according to laboratory parameters and PNI score; PNI scores were found to be significantly lower in patients who died and in patients admitted to the ICU (p=0.005, p<0.001). There was no significant difference between PNI scores and the presence of pneumonia on thorax CT. CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the ICU, and in patients who died (p=0.022, p=0.042, p<0.001, p<0.001, p<0.001, p<0.001, respectively). (**Table 2**)

When we look at the whole group, there was a significant negative correlation between PNI score and NLR (r=-0.399; p<0.001), and CRP/albumin ratio levels (r=-0.288; p<0.001) (**Table 3**). There was a significant negative correlation between PNI score and length of ICU stay, and length of hospital stay (r=0.170;p=0.009, r=0.274;p<0.001). There was a significant positive correlation between CRP/albumin ratio and NLR values (r=0.202; p<0.001), and between CRP/albumin ratio and length of ICU stay (r=0.134; p=0.041). (**Table 4**) In the ROC curve for the CRP/albumin ratio variable of COVID-19 patients who died, the area under the curve is 0.851, with a standard error of 0.011 (p<0.001). The cut-off point for CRP/albumin ratio is 1.09. The sensitivity of this value was 94.6%, and the sensitivity was 74.1%. (**Table 5**). The ROC curve is shown in **Figure 1.**

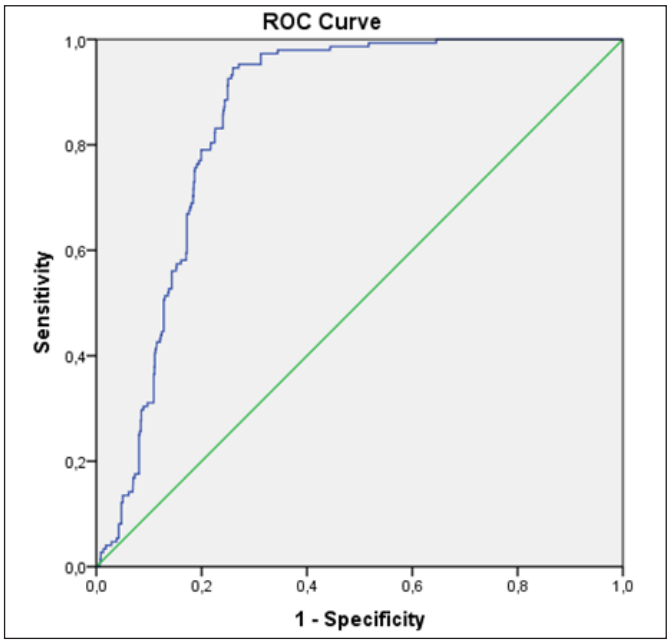

Figure 1. ROC curve analysis of CRP/albumin value variable of COVID-19 patients who died

Table 1. Distribution of selected baseline characteristics and laboratory parameters of whole group and by gender

	All Patients (n=1579)	Females(n=755, %47.8)	Males(n=824, %52.2)	p
Age (Year) (Median)	54 [43-65]	55 [44-66]	53 [41-64]	0.002[a]
Pneumonia on thorax CT				0.022[b]
Yes	1357 (85.9%)	633 (83.8)	724 (87.9%)	
No	222 (14.1%)	122 (16.2)	100 (12.1%)	
Hospitalized in				<0.001[b]
Ward	1346 (85.2%)	677 (89.7)	669 (81.2%)	
ICU	233 (14.8%)	78 (10.3)	155 (18.8%)	
Result				0.004[b]
Heraled	1431 (90.6%)	701 (92.8)	730 (88.6%)	
Exitus	148 (9.4%)	54 (7.2)	94 (11.4%)	
Length of ICU stay (day)	10 [7-16]	10 [7-15.25]	11 [7-17]	0.466[a]
Length of Hospital Stay (day)	7 [6-10]	7 [6-9]	7 [6-11]	0.006[a]
CRP	1.43 [0.29-5.35]	1.21 [0.25-4.85]	1.67 [0.34-5.97]	0.023[a]
Leukocyte	6.15 [4.70-8.00]	6.20 [4.80-8.00]	6.10 [4.62-8.00]	0.872[a]
Neutrophil	3.64 [2.57-5.00]	3.70 [2.59-5.00]	3.56 [2.54-4.99]	0.314[a]
Lymphocyte	1.45 [1.01-1.92]	1.45 [1.04-1.93]	1.43 [0.99-1.92]	0.274[a]
Albumin	3.72 [2.82-4.12]†	3.82 [2.82-4.12]†	3.70 [2.82-4.12]†	0.245[a]
NLR	2.57 [1.72-3.84]	2.63 [1.72-3.76]	2.51 [1.72-3.88]	0.948[a]
CRP / Albumin	0.41 [0.07-1.59]†	0.36 [0.06-1.49]†	0.48 [0.09-1.70]†	0.016[a]
PNI	44.65 [37.35-49.05]†	44.90 [37.45-49.25]†	44.37[37.01-48.85]†	0.346[a]

a Mann-Whitney test, b Chi-Square Test, p<0.05 was considered significant for all statistical analyses. ICU: Intensive care unit, CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index.

Table 2. Distribution and comparision of pneumonia on thorax CT, hospitalization status, treatment results according to the Prognostic Nutritional Index and blood test values

	Leu	Neu	Lymp	CRP	Alb	NLR	CRP/Alb	PNI
Pneumonia on Thorax CT								
Yes	6.10 [4.70-8.00]	3.63 [2.59-4.95]	1.45 [1.01-1.94]†	1.50 [0.30-5.69]	3.82 [2.82-4.12]	2.54 [1.74-3.73]	0.43 [0.08-1.62]†	44.50 [35.70-48.16]†
No	6.50 [4.87-8.00]	3.78 [2.35-5.12]	1.39 [1.02-1.83]	0.94 [0.20-4.25]	3.72 [2.82-4.12]	2.79 [1.63-4.24]	0.34 [0.06-1.18]†	44.65 [37.45-49.05]†
p	0.211	0.536	0.468	0.022	0.077	0.406 a	0.042 a	0.256 a
Hospitalised in								
Ward	6.18 [4.80-7.80]	3.64 [2.62-5.01]	1.48 [1.04-1.95]	1.03 [0.20-3.72]	3.82 [2.82-4.12]	2.56 [1.70-3.85]	0.32 [0.05-1.00]†	45.35 [37.73-49.50]†
ICU	6 [4-11]	3.74 [2.00-4.90]	1.27 [0.78-1.74]	6 [4-9]†	3.60 [2.82-4.00]	2.58 [1.80-3.71]	1.92 [1.28-2.84]†	41.25 [33.60-44.92]†
p	0.084	<0.001a	<0.001a	<0.001a	<0.001a	0.606 a	<0.001a	<0.001a
Result								
Healed	6.10 [4.60-7.70]	3.57 [2.48-4.93]	1.44 [1.00-1.91]	1.10 [0.22-4.00]	3.82 [2.82-4.12]	2.57 [1.70-3.84]	0.34 [0.06-1.15]†	45.10 [36.55-49.30]†
Exitus	8 [6-12]	4 [3-5]	1.55 [1.16-1.96]	8 [6-11]	3.80 [3.50-4.00]	2.58 [1.86-3.73]	2.28 [1.67-3.13]†	42.62 [40.46-45.10]†
p	<0.001a	0.001a	0.056	<0.001a	0.522	0.548 a	<0.001a	0.005a

a Mann-Whitney test, p<0.05 was considered significant. ICU: Intensive care unit, CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index, Leu: Leukocyte, Neu: Neutrophil, Lymp: Lymphocyte, Alb: Albumin

Table 3. Correlation analysis of PNI scores with other parameters

	Correlation coefficient (r)	P
Spearman's Rho		
NLR	-0.399	<0.001
CRP/Albumin	-0.288	<0.001
Length of ICU stay	0.170	0.009
Length of Hospital Stay	0.274	<0.001

P<0.05 was considered significant. ICU: Intensive care unit, CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index

Table 4. Correlation analysis of CRP/albumin ratio levels with other parameters

	Correlation Coefficient	P
Spearman's Rho		
NLR	0.202	<0.001
PNI	-0.288	<0.001
Length of ICU stay	0,134	0.041
Length of Hospital Stay	0.096	<0.001

P<0.05 was considered significant. Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index, ICU: Intensive care unit.

Table 5. ROC curve analysis of CRP/albumin ratio variable of COVID-19 patients who died

AUC(%95 Confidence Interval)	Cutt-Off	Standard Error	P	Sensitivity (%)	Specificity (%)
0.851 (0.830-0.872)	1.09	0.011	<0.001	94.6	74.1

P<0.05 was considered significant.

DISCUSSION

There is a close relationship between nutrition, immune system and infections. A healthy nutrition is essential for the development of immune response and protection from infections. A healthy diet can prevent viral infections by optimizing the immune response. On the other hand, malnutrition impairs the immune system, suppresses its functions and increases the risk of infection. It is known that malnutrition impairs the immune response, especially by affecting the cell-mediated immune system (9). Therefore, malnutrition leads to decreased immunity, which causes nosocomial infections and increases the morbidity and mortality associated with infections (10). The PNI score, calculated from albumin and lymphocyte levels, is an objective indicator of inflammatory and nutritional status. And the PNI is a parameter that has been confirmed to have prognostic value in cardiovascular diseases, malignancies and some infectious diseases such as infective endocarditis, mycobacterial infections (6,11-14) In this study, we used the PNI score to investigate the effect of nutritional status on the course of the disease in COVID-19 patients. There are not enough studies on COVID-19 and the nutritional status of patients. And there is not enough data in the literature about the relationship between COVID-19 and PNI. To our knowledge, this current study is the most comprehensive study which evaluates relationship between PNI or nutritional status of patients and COVID-19 disease severity.

In our study, which included 1579 patients, we found that the PNI score was statistically significantly lower in COVID-19 patients admitted to the intensive care unit and in patients who died. In other words, the PNI score was found to be lower in patients who needed admission to the intensive care unit and died due to severe COVID-19. In a study by Wang Z et al. (15) on 101 COVID-19 patients in China, the PNI score was found to be significantly lower in patients with severe COVID-19

disease. In a study conducted by Wang R et al. (16) on 450 COVID-19 patients in China, the mortality rate was found to be higher in patients with a low PNI score, and the PNI score was found to be an independent risk factor for mortality. In the study conducted by Yildirim A et al. (17) on 187 COVID-19 patients in Turkey, PNI score was found to be an independent predictor of mortality in hospitalized patients.We found similar results with the studies we mentioned in this current study.

Since the PNI score is calculated according to albumin and lymphocyte levels, we can explain these results over these two parameters as follows. The cytokine storm characterized by the release of large amounts of cytokines, especially interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) is associated with the severity of the disease (18,19). As in those with nutritional deficiencies, there may be a decrease in serum albumin level as a result of suppression of the synthesis ability of hepatocytes due to the increase in inflammatory cytokines such as IL-6 and TNF-α (20). In other words, low albumin level is an indicator of adverse processes such as tissue damage, cytokine storm, consumption due to hypermetabolic effect in COVID-19 patients. Low albumin levels in COVID-19 patients may exacerbate pulmonary edema by causing intravascular fluid exudation and accelerate the development of acute respiratory distress syndrome (ARDS) (21). Another component of the PNI score is the lymphocyte level. In COVID-19 disease, it is thought that there is a decrease in lymphocyte count due to direct attack of the virus on lymphocytes, dysfunction in antigen presenting cells (APC), or apoptosis due to excessive cytokine secretion (22). Lymphopenia was found to be an independent risk factor for mortality in COVID-19 patients (23).

In our study, CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the intensive care unit, in patients who died. Similarly, in many studies, CRP and CRP/albumin ratio levels were found to be a good prognostic indicator in COVID-19. High levels of CRP and CRP/albumin ratio were associated with higher hospitalization rates, higher ICU admission rates, and higher mortality rates. (24,25) CRP and CRP/albumin are well-known parameters in predicting the prognosis of infections. CRP elevation is already an expected finding in infectious diseases. We have mentioned above the possible causes of low albumin. Based on these, CRP and CRP/albumin ratio can also be used as good parameters to predict the clinical course in COVID-19. Also, in this current study, we found that there was a significant negative correlation between PNI scores and CRP/albumin ratio levels. The increase in the CRP/albumin ratio and the decrease in the PNI score were correlated in demostrating the clinical course. We think that this supports the importance of a low PNI score in predicting poor clinical course in COVID-19 patients.

Using the PNI score in COVID-19 patients, we investigated whether there is a relationship between the nutritional status of the patients and their clinical course. We found a higher mortality rate and higher ICU admission rate in patients with low PNI scores. We also found that patients with higher CRP and CRP/albumin ratios had a worse prognosis. We found a negative correlation between the PNI score and CRP/albumin ratio. PNI score, as a reflection of nutrition and inflammatory status in COVID-19 patients, can be used as a good parameter in showing the clinical course. However, more reliable results can be obtained with multicenter and more comprehensive studies to be conducted in the future.

CONCLUSION

In this study, we used the PNI score to show the nutritional status of the patients, we found that the PNI score was significantly lower in COVID-19 patients admitted to the intensive care unit and in patients who died. In other words, the PNI score was found to be lower in patients who needed admission to the intensive care unit and died due to severe COVID-19. In COVID-19 patients with a low PNI score, COVID-19 may be more severe and the clinical course may be worse. Therefore, patients with poor nutrition or low PNI scores should be followed up more carefully. CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the intensive care unit, and in patients who died. High CRP and CRP/albumin ratio levels and low PNI scores can be used to predict poor clinical course in COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital Ethics Committee (Date:10/03/2021, Decision No: 2020/123).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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